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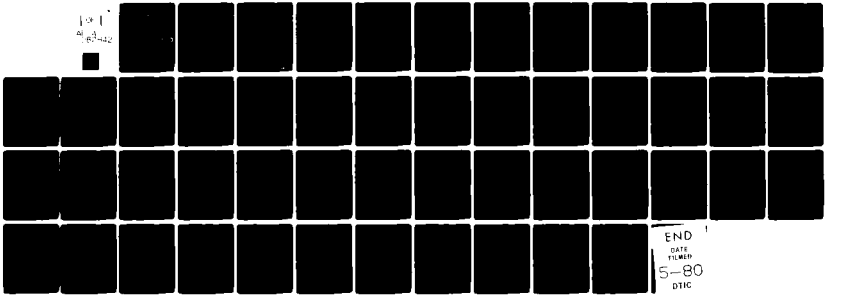

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Approaches to the nutritional management of infectious disease problems can be summarized in a series of guidelines and therapeutic steps in most clinical situations.
Body defensive mechanisms that prevent or minimize infectious illnesses seem to function best when a patient is in normal nutritional balance. Deficits or excesses of nutrients may predispose to an increased risk of infection or to an infection of increased severity.

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Although nutritional management during the therapy of most infections falls into the realm of secondary or supportive care, on rare occasions immediate correction of a nutritional abnormality may be of life-saving importance. It should then take precedence in the management of the illness. These emergency situations generally involve the correction of severe fluid and electrolyte or acid-base abnormalities. Severe hypoglycemia or anoxia must also be corrected without delay.

Chapter 22

Infectious Diseases

William R. Beisel*

An updated version of this chapter

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William R. Beisel

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Chapter 22

INFECTIOUS DISEASES

William R. Beisel

I. INTRODUCTION

A generalized infectious illness causes widespread metabolic responses in the host and in addition, leads to nutritional deficiencies. Localized infections may also result in metabolic and nutritional derangements, if the accompanying inflammatory response is of sufficient magnitude and severity.

During the first decades of this century, the medical management of infectious illnesses consisted solely of symptomatic therapy. Much importance was placed on dietary aspects of treatment. However, the close attention given to nutritional management diminished with the advent of the antibiotic era. As various new antimicrobial agents were recognized, the nutritional or dietary aspects of therapy were either neglected or relegated to an occasional role (7).

Observations in man and a variety of animal species indicate that deficiencies of isolated nutrients or generalized forms of protein-energy malnutrition may result in an impairment of host defensive mechanisms (1, 9, 15). On the other hand, infectious illnesses produce losses of body constituents that can lead to nutritional deficiencies. Thus, there is a tendency for a sequence of infection and malnutrition to develop into a synergistic cycle, with each new infection causing more profound nutritional deficits. These can, in turn, predispose the host to secondary infections. Such a vicious cycle occurs most often in young children of underdeveloped nations and helps account for their high mortality rates (9).

During an infection, some nutrients are lost from the body because of negative body balances (1, 5). Other nutrients are lost functionally because of metabolic and biochemical responses to hormonal stimuli (1). As detailed below, functional forms of nutrient loss include increased utilization, diversion from normal pathways of metabolism, or sequestration within body pools or depots in a manner that renders them temporarily unavailable for utilization.

To help develop a comprehensive nutritional plan for assisting in the therapy of infectious diseases, this chapter reviews underlying biochemical, metabolic, and hormonal mechanisms that account for the loss of body nutrients. By understanding these mechanisms and predicting their onset, magnitude, and duration, the thoughtful clinician should be able to anticipate probable nutritional deficits. This should help in planning appropriate measures for supportive care. In infectious diseases for which specific antimicrobial therapy is neither available nor effective, the clinician is faced with an even more important need to use nutritional measures as a key aspect of supportive management.

II. FORMS OF NUTRIENT LOSS DURING INFECTION

II.A. NEGATIVE BODY BALANCES (ABSOLUTE LOSSES)

Studies in volunteers have documented the changes in body balances of many nutrients during the course of bacterial, viral, or rickettsial diseases (5). Information has been obtained concerning the time of onset, magnitude, and sequential patterns of response during the prodromal and early febrile periods of acute infectious illnesses. Although these prospective studies include only a small variety of brief uncomplicated infections, such information can assist in the interpretation of data

derived during infections of overwhelming severity or a chronic protracted nature.

II.A.1. STEREOTYPIC PATTERNS OF ABSOLUTE LOSS

The most conspicuous nutritional consequence of infectious illness is an absolute loss of body constituents. This is shown clinically by loss of body weight and muscle tone and a progressive wastage of muscle mass and body fat. These losses are associated with negative body balances of the principal intracellular elements, including nitrogen, potassium, magnesium, inorganic phosphorus, zinc, and sulfur (5). Losses of nitrogen serve as a prototype for losses of the other intracellular components.

Negative nitrogen balances do not begin during the incubation period of an infection or even during the first day fever. However, once a febrile response is fully established, body balances become negative. Measured losses of nitrogen and other intracellular elements then exceed their respective intake values. As an acute infection persists, additional daily losses lead to a progressive depletion in body content of many elements. A self-limited mild viral illness induces losses of about 20 g nitrogen; if promptly treated, generalized tularemia may cause losses of 40-60 g; and untreated malaria can produce losses of 80-100 g. Losses of other intracellular elements are proportional to those of nitrogen.

Absolute nutrient wastage during hypercatabolic illness produces changes that overshadow other metabolic responses of the body. These catabolic losses are qualitatively similar during febrile illnesses caused by many different microorganisms. They represent a consistent stereotyped host response to illnesses of relatively short duration. Not

all elements follow the pattern of cumulative wastage seen with the principal intracellular elements. Although losses of sodium and chloride occur at the onset of a febrile infection, hormonal mechanisms quickly come into play to cause urinary retention of salt during the febrile phase of acute infections. The body then tends to retain water as well as salt.

Thus, body composition during a severe generalized infection is altered by a combination of factors, including increased metabolic needs of body cells, a lessening of dietary intake, complex endocrine responses, an overall wastage of most body nutrients, and retention of salt and water. Portraying this situation during septic starvation, Moore et al. (11) comment, "the body cell mass quickly melts away into a hypotonic ocean of extracellular fluid."

II.A.2. FACTORS CONTRIBUTING TO NEGATIVE BALANCES

II.A.2.a. FEVER. Even though fever may support the function of body defensive mechanisms, fever is a major factor in initiating body nutrient losses. Such losses are provoked equally by infectious fevers or the induction of fever by mean of bacterial endotoxin or a hot, humid environment (2). For each degree centigrade elevation of body temperature, basal metabolic rates increase by 11-13%. In addition, fever produces other direct losses via sweat. The magnitude of catabolic loss appears proportional to the severity and duration of fever. However, a protracted fever causes smaller losses as the body becomes severely depleted. The catabolic losses resulting from a short illness may require several weeks for correction (2, 5).

II.A.2.b. ANOREXIA. Like fever, anorexia may also constitute a defensive measure during some infections. However, the anorexia experienced by most patients during an infection contributes to body deficits. Anorexia leads to a diminution in the consumption of foods and a reduced intake of calories, protein, vitamins, and other nutrients. If food intake is restricted to a comparable degree in a noninfected normal volunteer, metabolic processes readjust rapidly, endogenous nitrogen sources are conserved, greater amounts of energy are derived from fat depots, and the body diminishes its rates of loss of vital nutrients. In simple starvation, nitrogen-sparing responses are initiated which reduce losses to 3-4 g/day. Such responses do not generally occur in the presence of fever. Indeed, some febrile patients actually increase nitrogen losses via the urine to above-normal values despite the anorexia and diminished intake of food. Should diarrhea or vomiting develop, additional losses occur via the intestional tract. This combination of events leads to a measurable net loss of a large variety of nutrient during periods of acute infection.

II.A.2.c. ENDOCRINE RESPONSES. Hormonal responses during infection are generally of limited duration and magnitude.

II.A.2.c.(1). Adrenal Hormones. An increased secretion of adrenal glucocorticoid hormones begins with, or shortly before, the onset of fever. Increases in daily rates of cortisol production may reach values two to five times normal. Plasma cortisol loses its circadian periodicity and generally maintains concentrations near, or slightly above, usual peak morning values. The increase in glucocorticoid

secretion is accompanied by smaller increases in the output of adrenal ketosteroids and pregnanetriol. These ACTH-mediated adrenocorticoid responses do not persist beyond the onset of recovery. If an infection becomes subacute or chronic, the urinary excretion of adrenal steroids generally falls below normal.

The onset of septic shock or the progression of infectious illness to an agonal stage is often accompanied by steadily increasing plasma cortisol concentrations. High values result from a functional failure of hepatic enzyme systems that normally metabolize steroids. On the other hand, hemorrhage into the adrenal gland during bacterial sepsis or hemorrhagic viral diseases may cause glucocorticoid production to cease. If this occurs, cortisol and mineralocorticoid replacement therapy becomes an acute necessity.

Changes in aldosterone secretion do not coincide with those of cortisol. Increased production of aldosterone becomes evident only after fever has begun, and abates gradually in early convalescence. The increase in aldosterone secretion contributes to renal salt retention during acute infections. In addition, a tendency for excessive body water to accumulate during many severe infections has been attributed to inappropriate secretion of antidiuretic hormone.

II.A.2.C.(2). Thyroid Hormones. Changes in thyroid hormone economy are best evaluated in relation to the stage of an infectious process. A biphasic pattern of thyroid response seems evident. An accelerated disappearance rates of T_4 and T_3 from plasma occurs during early stages of infection. Changes in serum T_3 values may be accompanied by reciprocal changes in reverse T_3 and the binding of thyroid hormones to

serum proteins may be altered. These early changes suggest increased utilization, deiodination of thyroid hormones, or both, by peripheral tissues during fever and periods of increased phagocytic activity. A sluggish response of the pituitary-thyroid axis helps to account for the initially depressed T_3 and T_4 values, but eventually the thyroid is activated. Thus, during early convalescence, hormonal values may increase and the rate of T_4 disappearance may slow. These latter observations are in keeping with an eventual "overshoot" in thyroid gland activity in response to the earlier acceleration of hormone degradation. Further, thyroid glands from patients with overwhelming infections show histologic changes typical of increased secretory activity.

II.A.2.d.(3). Glucoregulatory Hormones. Hormones that influence carbohydrate metabolism are intimately involved in host responses during febrile illnesses. Fasting plasma concentrations of glucose, insulin, glucagon, cortisol, and even growth hormone tend to be increased (13). The hepatic production and release of glucose is accelerated as a consequence.

If carbohydrate tolerance is measured by means of a glucose load during early fever, the insulin responses and glucose disappearance rates show changes resembling those of maturity-onset diabetes. Elevated fasting glucagon values decline appropriately after IV glucose test loads, but growth hormone secretion seems to undergo an acute paradoxical stimulation (13). Catecholamine values are also increased during some infections, especially those accompanied by hypotension.

These combined hormonal responses initiate molecular mechanisms to release glucose from stored hepatic glycogen and to increase rates of gluconeogenesis from available substrates. An increased flux of

gluconeogenic amino acids, such as alanine, from muscle to plasma to liver supports this activity. The increase in hepatic gluconeogenesis may cause fasting hyperglycemia of 120-150 mg/dl despite an increased rate of glucose utilization by body cells. Newly produced glucose appears to serve as the principal fuel used by body cells for the extra energy requirements of fever. However, during overwhelming sepsis in newborns and in patients with severe liver damage, such as that due to viral hepatitis or yellow fever, glycogen reserves in liver and skeletal muscles become depleted and hypoglycemia may result. No specific enzyme failure has been identified in any biochemical pathway that could account for an agonal breakdown in carbohydrate synthesis in the absence of hepatocellular necrosis.

Other consequences of the unusual hormonal ratios seen during infection include a partial to complete inhibition of hepatic ketone production and a slowed release of free fatty acids from storage depots.

II.A.2.d. DURATION OF ILLNESS. If a febrile illness is of brief duration, negative balances are quickly reversed and the body begins to retain depleted nutrients. To reconstitute normal body composition, a patient generally develops positive balances for depleted nutrients in early convalescence. The magnitude and duration of positive balances appear to be determined by the type and quantity of dietary intake, as well as by the extent of cumulative deficits incurred during illness. For most uncomplicated minor illnesses, deficits are reconstituted within a period of several weeks in a manner similar to convalescent patterns of recovery after trauma. Recovery of depleted body stores may be assisted by a transient hyperphagic increase in appetite during convalescence. In some children, this is sufficient to permit

"catch-up" growth (1, 9), but a series of infections may cause severe growth retardation in young children.

Should an acute infectious process become chronic, daily nitrogen balances gradually become less negative each day. Thus, as day-by-day losses diminish, a chronically ill patient begins to return to a new equilibrium state, although at a wasted, cachectic level. The body can generally reconstitute such chronic losses if protracted infections are treated successfully.

II.A.2.e. SEVERITY OF ILLNESS. As a general rule, severe infectious illnesses produce greater nutritional insults than do mild ones. However, an overwhelmingly severe infection that leads to death in a matter of hours or days may run its course before an appreciable wasting of body tissue has a chance to occur.

II.A.2.f. LOCALIZATION OF INFECTION. The generalized stereotypic metabolic response to infection may be altered by processes that are localized in certain organs. For example, marked losses of fluid and electrolytes complicate diarrhea, important metabolic functions of the liver may be lost during hepatitis, and impaired pulmonary gas exchange and losses via sputum may occur in pneumonia.

II.B. FUNCTIONAL FORMS OF NUTRIENT LOSS

In addition to direct losses of body nutrients, metabolic and biochemical host responses produce several functional forms of nutrient loss (1). Functional losses are defined as the within-body losses due to metabolic or pathophysiologic responses. They include overutilization, diversion, or sequestration of nutrients. In facing the challenge of an

acute febrile illness, the body utilizes muscle protein, endogenous fuels, and other nutrients in an apparently inefficient and wasteful manner. On the other hand, the redirected metabolism may contribute to host defensive mechanisms. Nevertheless, these functional forms of loss add to the nutritional requirements of the body and must be considered when planning comprehensive therapy for infection.

II.B.1. OVERUTILIZATION OF NUTRIENTS

Overutilization of body nutrients is one example of functional wastage. Increased cellular needs for body fuel can virtually deplete carbohydrate stores during severe sepsis or endotoxemia. However, during uncomplicated infections, amino acids and other substrates for gluconeogenic activity are metabolized in sizable quantitities. The presence of fever has long been known to increase the metabolic rate of body tissues. An accelerated utilization of metabolized fuel by cells throughout the body is accompanied by accelerated rates of hepatic synthesis of cholesterol and triglycerides, degradation of liver and muscle glycogen, and the accelerated utilization of amino acids for glucose production.

An increased utilization of vitamins must also be anticipated. Severe infections in man may precipitate clinically apparent vitamin deficiency states, e.g., scurvy, beriberi, pellagra, or vitamin A deficiencies. Vitamin losses via urine during infection do not seem to account for such instances of overt vitamin deficiency. Of 14 vitamins studied during experimentally induced sandfly fever in volunteers, only vitamin B_2 showed an increased rate of urinary loss (3). Thus, a depletion of vitamin stores in the tissues during infectious illnesses or the decline in blood concentrations of several vitamins can be

ascribed to accelerated utilization of vitamins by body tissues rather than to measurable excretory losses.

II.B.2. DIVERSION OF NUTRIENTS

The second form of functional wastage involves the diversion of nutrients from their usual metabolic pathways. The infectious process stimulates a marked increase in the rate of uptake of plasma amino acids by the liver. In addition to their enhanced hepatic utilization for gluconeogenesis, the exaggerated movement of amino acids into the liver is followed by rapid incorporation into newly synthesized acute-phase reactant plasma proteins. These proteins include α_1-antitrypsin, seromucoid, haptoglobin, ceruloplasmin, C-reactive protein, and others. Although these proteins appear to modulate inflammatory and immunological responses, their synthesis has a high cost in terms of amino acid and energy expenditures.

Some of the amino acids that enter the liver in excess are used for incorporation into newly synthesized hepatic enzymes, some are diverted for metallothionein formation, and some enter normal metabolic pathways, but in excess amounts. An example of the last is the accelerated metabolism of tryptophan via the kynurenin pathway during many infections, especially typhoid fever (1). A variety of metabolic products of tryptophan are then excreted in excess and lost from the body as urinary diazo reactants.

II.B.3. SEQUESTRATION OF NUTRIENTS

Another form of nutrient wastage during infection is represented by the temporary sequestration of nutrients in relatively inaccessible forms (1, 4). For example, an increased movement of iron from plasma to

liver is a characteristic host response in many infectious diseases, especially those accompanied by a prominent inflammatory response. Iron in the form of hemosiderin or ferritin then accumulates in hepatic storage depots. Sequestered iron is not readily reutilized for the formation of hemoglobin as long as the infection persists. This sequestration eventually leads to the "anemia of infection," which resembles iron-deficiency anemia in its peripheral red blood cell and serum iron values. Unlike iron-deficiency anemia, however, supplies of iron accumulate in body stores during infection, and total serum iron-binding capacity tends to decrease rather than to increase.

The combination of low serum iron values with increased concentrations of unsaturated transferrin appears to have some protective value for the host (1). Because ferric iron is extremely insoluble in body fluids, many bacteria synthesize siderophores to acquire the iron they need to proliferate. The siderophores have association constants high enough to compete successfully with saturated transferrin for iron (1). However, the increased concentration of unsaturated transferrin in an infected host makes it difficult for bacteria to acquire sufficient iron to carry out their normal metabolic functions, to achieve logarithmic growth patterns, or to produce certain toxic products (1, 4).

Zinc is also sequestered within the liver. After an increased flux into liver, the zinc is sequestered within hepatic cells by newly synthesized metallothioneins and serum zinc values decline.

Sodium can also become sequestered in various body cells during severe illness, especially in infections accompanied by marked acidosis.

II.C. CELLULAR NEEDS

An infectious illness is accompanied by hypermetabolism and accelerated utilization of cellular energy. A sudden increase of energy expenditure occurs whenever a phagocyte is activated. A burst of glycolytic energy production develops when neutrophils begin to take up and kill invading bacteria or other microorganisms. Other body cells need to be supplied with energy from circulating metabolic fuels to perform their infection-stimulated functions.

To meet the added demands for cellular energy, the body utilizes its molecular machinery for producing glucose. This process involves increased secretion of hormones such as glucagon, the adrenal glucocorticoids, and the catecholamines; these hormones combine to induce two related patterns of response within the liver. The enzymes that control the release of glucose from glycogen stores are activated. In addition, the rate of production of glucose is accelerated, utilizing gluconeogenic amino acids, lactate, pyruvate and glycerol as substrates.

Well-controlled, insulin-dependent diabetic patients who develop an acute infection are likely to develop hyperglycemia with glycosuria. It has long been taught that these diabetic patients need additional amounts of insulin if they develop an infection. Infection-induced hyperglycemia has traditionally been thought to represent an impairment of the ability of insulin to act on peripheral body cells. This is accompanied during infection by great increases in both production rates and body pool sizes of glucose, with accelerated glucose turnover within the enlarged pools. The body appears willing to sacrifice scarce amino acids and other nutrient precursors to provide cells with more than adequate concentrations of glucose during periods of acute febrile

illness. This response begins within several hours of the onset of fever (13).

In addition to producing additional amounts of glucose during infection, the liver also speeds up its synthesis of both cholesterol and fatty acids from acetate and other precursors. Excess triglycerides are formed within the liver; these either accumulate in lipid droplets within hepatic cells or are secreted into the plasma (1).

II.D. SUMMARY OF NUTRITIONAL CHANGES

Even the least complicated of generalized infections stimulate a wide variety of metabolic and nutritional responses. These result in expenditures or losses of essential body nutrients. Loss of body weight is the combined result of fever-induced hypermetabolism, impaired appetite, and complex series of hormonal and physiologic responses that lead to absolute losses of body nitrogen, potassium, magnesium, zinc, and sulfur. There are increased expenditures of calories, vitamins, and amino acids. Host defensive mechanisms require increased formation of new cells, such as those of the phagocytic and lymphoid series, the synthesis of intracellular enzymes, hormones, other products, and new serum proteins, including the acute-phase reactants, specific antibodies, complement, interferon, and fibrinogen.

Approaches to nutritional therapy should be based on the metabolic responses known to occur during an infection. The absolute loss of body nutrients can be reduced during an infectious illness and should be corrected early in convalescence. Excessive nutrient requirements can be reduced by therapeutic measures to diminish the febrile response and eliminate invading microorganisms.

III. GENERAL MANAGEMENT OF INFECTIOUS PROBLEMS

III.A. INCIDENCE OF INFECTIOUS DISEASES

Infectious diseases occur at every age and in all population groups. Infection-related problems also play a secondary or complicating role in other varieties of medical, surgical, or pediatric illness. Infectious disease problems are of greatest importance at the extreme ends of the normal human life span. Although no age group is free of infectious diseases, middle-aged persons generally have the lowest incidence of serious infections.

Contrary to the hopes and expectations that accompanied the advent of the antibiotic era, infectious diseases have not been eliminated from the medical scene, even in the most advanced societies. Also, although advances in medical and surgical technology have generally increased life expectancy, they have sometimes introduced nutritional debilities, immunologic defects, and other iatrogenic factors that break down natural host defensive mechanisms. As a result, the older classic infectious disease have been replaced in major hospital centers by an increased incidence of opportunistic infections. This unanticipated consequence of medical progress has forced practitioners of all medical specialty fields to face new varieties of infections caused by bacteria, fungi, viruses, or parasites not previously thought to be widely pathogenic or of more than incidental concern.

General improvements in sanitation and vigorous programs of preventive medicine and public health have shown that it is possible to control or virtually eliminate many of the epidemic or endemic infectious diseases of previous years. Small pox may never be seen again.

Development of safe and effective vaccines has gone far toward controling such epidemic diseases as diphtheria, pertussis, measles, and poliomyelitis. The incidence of tuberculosis, enteric bacterial, parasitic and venereal diseases have been minimized in the highly industrialized nations. Although these advances have lessened the danger from common communicable killers of previous generations, infectious diseases continue to cause death and debility in modern societies. Further, infectious diseases account each year for more deaths on a global scale than any other form of illness.

Thus, despite the availability of many antibiotic, public health, and immunoprophylactic measures, infectious diseases are likely to remain a continuing and serious health problem. In addition to the growing incidence of opportunistic infections in advanced medical centers, the reemergence in some localities of venereal diseases, malaria, and poliomyelitis show how easily an apparently well-controlled situation can be reversed unless prophylactic and public health measures are pursued with continuing diligence.

Of major concern is the well-recognized synergistic cycle that relates infectious disease to malnutrition. The prevalence of malnutrition and infection continues to produce high childhood mortality rates in underdeveloped nations, especially those with tropical and subtropical climates. This problem will remain unsolved in the presence of world population growth and a continuing failure to produce or distribute sufficient food for all people (9).

III.B. THERAPEUTIC MODALITIES

The obvious aim of therapy is to control and eliminate invading microorganisms before serious illness or lasting complications can

occur. The first line of medical management is to identify the causative agent--if this is possible--and define effective chemotherapeutic or immunotherapeutic approachs.

Proper antimicrobial management involves the selection of the drug and dosage schedules most likely to produce complete and rapid control of the infection without causing untoward secondary effects. Exact identification of the infecting microorganism and its range of sensitivity are valuable if these can be obtained. However, if the severity and course of an infection require that therapeutic decisions be made in the absence of such information, judgements must be based on a careful evaluation of the available clinical and laboratory findings.

Some infections require the use of active or passive immunotherapeutic procedures rather than antimicrobial drugs, and some must still be managed without such benefits.

Nutritional modalities of therapy are usually, and most appropriately, classified among the secondary forms of general supportive therapy. Nevertheless, this support can be of benefit to patients receiving specific antimicrobial therapy. For infectious diseases that lack specific therapy, nutritional support is of even greater importance. Nutritional therapy is especially useful in patients with viral illnesses or in individuals with preexisting nutritional deficiencies. In rare instances, such as fulminant cholera or hepatitis-associated hypoglycemia, rapid correction of life-threatening physiologic or biochemical imbalances can be achieved only through the administration of an essential nutrient such as water, glucose, or electrolytes. Under such conditions, emergency replacement therapy, a form of nutritional management, must be given first priority.

IV. NUTRITIONAL MODALITIES OF THERAPY

IV.A. DIRECT NEEDS

There are relatively few instances in clinical medicine where nutritional modalities of therapy are of specific direct importance in managing an immediate life-threatening problem. However, these situations must be recognized quickly and treated effectively when they occur. Perhaps the best example of such an emergency requirement is the need to correct the massive loss of body fluids and electrolytes that occur during fulminant diarrhea. In patients with cholera or severe Escherichia coli enterotoxemia, intestinal losses of water, sodium, chloride, and other nutrients can lead quickly to hypovolemic shock and death.

Other forms of acute nutritional imbalance may occur in infections that damage key body cells and precipitate secondary depletions of body nutrients or an accumulation of toxic metabolites. If of sufficient severity, infectious hepatitis may produce hypoglycemia or hepatic failure. Severe hypoglycemia is also a common danger in neonatal infants with sepsis. Life-threatening hypoglycemic shock can be suspected through clinical signs, diagnosed by blood glucose analysis, and corrected with glucose infusions. In contrast to the infection-induced depletion of an essential body nutrient such as glucose, the accumulation of potentially toxic metabolic products can occur in patients with liver failure of infectious origin. This can be managed as outlined in Chapter 20.

IV.B. SECONDARY AND SUPPORTIVE MODALITIES

Supportive nutritional therapy is based on the anticipated loss of nutrients during an infectious illness. The practitioner should actively seek to prevent or lessen the harmful consequences of nutritional wastages. Supportive therapy should be initiated concurrently with antimicrobial measures.

IV.B.1. FEVER

Catabolic losses in a patient with an infectious process generally do not begin until after the onset of the febrile phase of illness. Thereafter, the duration and severity of fever influence the magnitude of both absolute and functional losses. Lessening of fever by antipyretic drugs or by direct physical methods serves to reduce the nutritional needs for the excessive energy production required by the presence of fever. Control of fever also reduces dermal losses of nutrients via sweat.

When fever is not controlled, its impact must be taken into account when calculating daily caloric and protein needs.

IV.B.2. ANOREXIA

A major nutritional problem associated with acute infectious illness is the presence of anorexia. This is often compounded by overt nausea and vomiting. It then becomes almost impossible for a patient to maintain a normal oral intake of fluids, calories, protein, and other nutrients. This problem can not be solved by ordering a properly calculated dietary intake to be delivered to the bedside or by instructing a sick patient to eat the quantities and varieties of foods calculated to meet nutritional needs. Kindly and purposeful encouragement by an

attentive nursing staff or family is similarly ineffective in many instances. However, a sick patient should be offered soft or liquid foods of high nutrient and caloric value. When marked anorexia and nausea severely restrict food intake, anticipated deficits should be minimized by using the parenteral route.

IV.B.3. ESTIMATION OF CALORIC NEEDS

The caloric needs of a patient with an infectious illness should include the normal recommended daily dietary allowance plus extra amounts needed because of fever. Daily requirements can be derived from standard table values (see Table A-1), and the added needs can be calculated according to the amount of fever (7% increase for each °F of elevation).

Thus, a 35-year-old male weighing 70 kg, who ordinarily requires an energy intake of 2,700 kcal (Table A-1), with a body temperature 3°F above normal, would require 2,700 kcal, plus 3 x 7% of 2,700 kcal. This amounts to 2,700 plus 567 kcal, or 3,267 kcal/day. Alternatively a febrile adult could be given 30-40 kcal/kg/day, a child, 100-150 kcal/kg/day, and an infant, 200 kcal/kg/day (1).

Caloric adequacy during an acute illness can also be determined by changes in body weight. Body weight changes during infection should be evaluated with the knowledge that weight loss may be masked by the tendency for febrile patients to retain salt and water. Water retention of one or more kilograms may occur during a febrile illness and obscure equivalent losses in tissue mass. The true extent of body loss may not become apparent until after the fever, when postfebrile diuresis causes excessive fluid to be excreted. If caloric intake has not kept

pace with body needs during an illness, deficits should be made up as early as possible in the convalescent period.

IV.B.4. PROTEIN REQUIREMENTS

Every host defensive mechanism is ultimately dependent on the protein-synthesizing capabilities of individual cells. Nevertheless, the body will sacrifice amino acids through functional diversions to provide for total caloric needs. Thus, the protein requirements of a febrile patient will depend in part on the daily availability of caloric energy.

If energy intake is inadequate, amino acids derived from dietary protein or existing body pools are diverted to meet of energy needs rather than for incorporation into the structure of new proteins or for metabolic uses unique for each amino acid. Since metabolic energy must be expended to deaminize amino acids for carbohydrate synthesis, the use of amino acids for calorigenesis is doubly wasteful.

In the presence of fever, the body fails to initiate the metabolic adjustments used to conserve body nitrogen during periods of simple starvation. Nevertheless, it is possible to reduce excessive losses of body nitrogen in febrile patients by increasing the intake of total calories. Although the extra energy needs should be met preferably by adding non-nitrogenous sources of calories to the daily nutrient intake, the body should not be forced to depend on endogenous tissue protein for its amino acid requirements.

Exact protein requirements have not been determined during periods of fever. However, a consensus holds that the desirable nitrogen intake should be 1.5 g/kg/day for febrile adults and 3.0 g/kg/day for

febrile children (1). The nitrogen source should include a balanced supply of essential amino acids.

Several simple methods are available for estimating protein requirements. Urea nitrogen assays can be performed by most clinical laboratories on 24-hour urine specimens. A daily urea nitrogen excretion value plus 4 g (2 g for non-urea nitrogen in urine and 2 g for stool nitrogen) provide a reasonable estimate of nitrogen loss. If this value is compared with an estimate of nitrogen intake based on table values, a rough idea of nitrogen balance can be obtained. Measurements of serum albumin concentration, skin-fold thickness, and midarm muscle circumference are also of value in determining the adequacy of protein intake, especially in patients whose illness is protracted.

IV.B.5. ACID-BASE STABILIZATION

Infectious diseases cause a variety of changes in acid-base equilibrium. Different pathogenic mechanisms may allow metabolic acidosis, metabolic alkalosis, respiratory alkalosis or respiratory acidosis to develop singly or in complex physiologic derangements. The clinician must be aware of these possibilities to determine if corrective therapy is required during illness, or replacement therapy during convalescence.

IV.B.5.a. RESPIRATORY EFFECTS. The pathophysiologic course of an infectious process or its complications may cause complex respiration-induced changes in acid-base equilibrium. Fever is typically accompanied by increased cardiac and respiratory rates. Fever-induced hyperventilation leads to an increased rate of gas exchange within the lungs and causes an exaggerated loss of dissolved carbon dioxide from

the blood. This produces uncompensated respiratory alkalosis during periods of rising fever. Respiratory alkalosis may persist as long as tachypnea exists in the presence of a free exchange of pulmonary gases. Rarely, however, is respiratory alkalosis sufficient to produce carpopedal spasm or require therapy.

On the other hand, if pulmonary consolidation prevents adequate gas exchange, hypoxia and respiratory acidosis are observed. Impaired gaseous exchange is also a problem in botulism, poliomyelitis, or tetanus, diseases which impair neuromuscular components of pulmonary function. Under these conditions, oxygen becomes a nutrient that must be supplied (see Ch. 31).

IV.B.5.b. METABOLIC EFFECTS. Metabolic factors influence acid-base equilibrium if an infectious process becomes chronic or severe. In high fever or prolonged illness, the generation of lactic acid and other metabolic products exceeds the capacity of the body to dispose of them. If the quantity of acid metabolites is sufficiently great, metabolic acidosis begins to emerge. If bacterial sepsis produces hypotension and vascular stasis, impaired oxygen transport leads to cellular hypoxia, exaggerated formation of lactic acid, and a further increase in the severity of metabolic acidosis.

Diarrheal diseases can produce two different additional varieties of acid-base imbalance. Since the lower small bowel and proximal colon contain intraluminal bicarbonate concentrations almost double those of plasma, massive diarrhea causes large losses of bicarbonate from the body. This loss of bicarbonate can lead acutely to metabolic acidosis, and can be treated by adding bicarbonate or lactate to replacement fluid

infusions. Bicarbonate should be replaced until the urine pH becomes alkaline.

In severe or chronic diarrheas, large amounts of potassium are also lost. If these losses are great, vacuolar degeneration of body cells may be observed histologically, especially in the renal tubules. A massive loss of body potassium will also produce severe metabolic alkalosis, which can persist for many months unless treated. The development of hypokalemic nephropathy and metabolic alkalosis can be prevented by replacement therapy with potassium. This essential nutrient can be provided using commercial solutions to provide 20-35 mEq of potassium per liter. During severe diarrhea, the massive losses of potassium can be treated by potassium-containing maintenance fluids given primarily to compensate for continuing losses of water. Residual or chronic deficits should be corrected with high-potassium foods during the convalescent period.

IV.B.6. ELECTROLYTE AND WATER REQUIREMENTS

An infectious process may lead to death from fluid imbalances ranging from severe overload to severe dehydration. Direct losses of salt and water occur in diseases accompanied by severe or protracted diarrhea, vomiting, or marked diaphoresis. In the absence of such direct losses, the body usually retains fluid and electrolytes. With severe illness, sodium may accumulate within poorly functioning cells; hyponatremia is then seen despite a normal total body content of sodium. Water retention due to inappropriate antidiuretic hormone secretion will increase the severity of hyponatremia. Appropriate therapy in the latter types of salt and water derangements requires a restriction of fluid and electrolyte intake. Thus, a patient with infectious illness

may have an emergency need for electrolyte replacement or may, on the other hand, be seriously harmed by fluid and electrolyte administration. An understanding of the pathophysiologic mechanisms leading to deranged fluid and electrolyte balance is therefore necessary when deciding on the proper therapeutic measures.

IV.B.6.a. SODIUM WASTAGE. The losses of body water and electrolytes during Asiatic cholera provide insight into the conceptual approaches required for planning optimal therapy for exaggerated forms of acute diarrhea. In massive diarrhea, the watery stools are virtually isoosmotic with plasma. Because stool losses are isoosmotic, water does not move from body cells to maintain the extracellular volume, and an immediate threat to life emerges due to depletion of circulatory volume and shock.

Losses of body water and electrolytes in equivalent isoosmotic amounts lead to extracellular dehydration without appreciable changes in the concentrations of plasma sodium in relation to plasma water. However, the extent of body dehydration can be assessed by clinical signs, together with high hematocrit values and increased concentrations of total plasma proteins in relationship to plasma water. This type of dehydration increases the specific gravity of both whole blood and plasma. Because plasma proteins may undergo a two-fold increase in concentration during severe cholera, measured sodium and chloride concentrations may appear to be diminished, if they are calculated and expressed, conventionally, on the basis of whole plasma values. To be physiologically accurate and therapeutically meaningful, electrolyte concentrations of such dehydrated patients must be recalculated to

reflect the high protein concentration and diminished amount of water present in the plasma.

Isoosmotic dehydration due to massive diarrhea must therefore be corrected by the use of isotonic replacement fluids (6). Emergency fluids are given rapidly to correct shock and acidosis, and to return hematocrit and plasma protein concentrations to normal. After initial rehydration, homeostasis is maintained by infusing solutions at a rate to match measured hourly stool volume losses. Potassium deficiency can be made up by mouth or by potassium-containing fluids.

Severely dehydrated hypotensive cholera patients may have pulmonary rales when first examined or may develop acute pulmonary edema during rehydration (6). If due to severe coexisting acidosis, this cardiopulmonary problem should be managed by the use of bicarbonate- or lactate-containing resuscitation fluids.

IV.B.6.b. SODIUM RETENTION AND SEQUESTRATION. Dehydration is not usually a problem in generalized infectious diseases that do not include diarrhea or massive vomiting. Rather, the onset of fever is accompanied by increased secretion of aldosterone and antidiuretic hormone. Acting in concert on distal renal tubular cells, these hormones cause the kidneys to retain both salt and water. Sodium and chloride may virtually disappear from the urine, and urine volume may be sharply reduced.

If the secretion of antidiuretic hormone persists in an inappropriate fashion, body water is retained even in the presence of declining plasma concentrations of both sodium and chloride. Because of the retention of salt and water in many infectious illnesses, it is generally unwise to administer saline in IV solutions. Further, if chronic metabolic acidosis develops, variable amounts of sodium may accumulate within body

cells. The sequestration of sodium within body cells is evidence of severe illness and is not easily reversed. The unwise administration of saline in an attempt to correct depressed serum sodium concentrations in such patients may have serious consequences, such as cerebral edema in children with meningoencephalitis.

Severe hyponatremia that cannot be explained by direct sodium losses should be managed by restricting salt and water intake until after the infectious process is controlled and serum sodium concentration begins to increase. This type of problem is most common in the aged, or in children with CNS infections, Rocky Mountain spotted fever, or other severe generalized infections. Daily fluid intake should be severely restricted. Body weight, urinary specific gravity and volume, and serum and urine values for sodium and osmolality should be measured each day; central venous pressures may need to be followed in some patients. When urinary specific gravity begins to decline and the daily urine volume increases, fluid intake can be liberalized.

IV.B.7. MINERAL AND TRACE ELEMENT REQUIREMENTS

Little direct information is available about the need to employ minerals or trace elements as therapeutic agents (4). For the present, the wisest course of action would seem to demand that natural foodstuffs be given--if possible--in adequate quantities during illness, and certainly during early convalescence, in an effort to correct or restore any infection-induced mineral or trace element imbalance or deficit.

IV.B.7.a. MAGNESIUM. Magnesium concentrations in serum may decline somewhat during the course of a generalized infection as the result of a dilutional phenomenon associated with the retention of body water. In

addition, metabolic balance studies in volunteers with relatively mild infections demonstrate negative balances of magnesium (5). These occur in close proportion to negative balances of nitrogen. Since potassium is also lost in generally proportional amounts, it can be postulated that these nitrogen-equivalent losses are derived from cellular pools. No data are available concerning the use of magnesium supplements in infectious illnesses, but they may be needed if there is a prolonged negative balance of this element, as during surgical complications that induce major losses of magnesium from intestinal drainage or burned surfaces.

IV.B.7.b. CALCIUM. Calcium concentrations in plasma may undergo a dilutional decline, but otherwise calcium metabolism does not seem to be influenced importantly by most infectious illnesses. However, body balances of calcium and other bone minerals do become negative if an infectious disease causes body immobilization or paralysis. Calcium accumulates in devitalized tissues, and the tendency for granulomatous tubercular lesions to become calcified is well known. Although a high calcium intake was employed in the preantibiotic management of tuberculosis, there is little to suggest that this mineral was of importance in arresting the disease. On the other hand, tuberculous patients may develop a sarcoidosis-like hypersensitivity to vitamin D; if this occurs, vitamin D and calcium intakes must both be carefully controlled to avoid hypercalcemia.

IV.B.7.c. PHOSPHORUS. Inorganic phosphate metabolism shows a complex variety of changes in different infectious illnesses. Unusually low serum concentrations of inorganic phosphate have been reported in

patients with gram-negative sepsis and in Reye's syndrome. Reduced serum phosphate concentrations may serve as a possible diagnostic indicator of sepsis. Serum phosphate values also decline rapidly but transiently during the early stages of fever, apparently as a secondary manifestation of respiratory alkalosis. Hypophosphatemia during an acute rise in body temperature is accompanied by the virtual disappearance of phosphate from urine and sweat. These changes occur too rapidly to be accounted for by parathyroid gland responses.

In volunteers with experimentally induced infections, body balances of phosphorus become negative (5). Like the negative body balances of potassium and magnesium, phosphate losses parallel quite closely the magnitude and timing of nitrogen losses.

The participation of organic phosphates in many aspects of intermediary metabolism is well recognized. Organic phosphate moieties and high energy phosphate bonds undoubtedly contribute at the cellular level to host responses to infection. Infection-related changes also occur in the activities of phosphatase enzymes contained in many body cells and serum. It is not known how these changes influence the outcome of an infection, and there is no direct evidence that the administration of phosphate as a single nutrient would be of clinical importance.

IV.B.7.d. IRON. Iron metabolism is markedly altered by infection. Many bacterial and viral infections as well as malaria cause red blood cell destruction. In addition, the concentrations of iron decline rapidly in serum at the onset of an infectious illness. This change appears to be due to a flux of iron from serum to liver. There, the iron becomes sequestered in cellular stores of hemosiderin and ferritin.

The initial acute decline in serum iron occurs without appreciable changes in serum iron-binding capacity. As a result, the quantity of unsaturated transferrin is increased in serum during the initial stages of infection. If an infectious process becomes chronic, serum iron values remain low and iron-binding capacity begins to decline slowly. The iron sequestered in tissue stores represents a form of functional wastage, inasmuch as the iron seems to be trapped and unavailable for reutilization in the synthesis of hemoglobin for new red blood cells. This infection-induced sequestration of iron, together with a tendency for red blood cell survival to be shorter, can give rise to the so-called "anemia of infection."

During chronic infections, the administration of iron by either oral or parenteral routes is ineffective in reversing the anemia of infection. If parenteral iron therapy is given while an infectious process remains active, administered iron also becomes sequestered in storage forms. Liver extract, the folates, or vitamin B_{12} are similarly without value.

Further, if parenteral iron therapy is used in children with kwashiorkor or protein-energy malnutrition, it can have disastrous consequences. The additional therapeutic iron serves to saturate the low serum iron-binding capacity common in protein-malnourished children. The presence of saturated transferrin in serum makes iron available to aerobic and facultative bacterial pathogens that may then proliferate rapidly to overwhelm the already impaired host defensive mechanisms of the malnourished child. Thus, if total serum iron-binding capacity is depressed in a malnourished child, iron therapy is actually contraindicated until protein repletion therapy has increased serum iron-binding capacity to normal values.

IV.B.7.e. COPPER. Concentrations of copper in serum usually show an increase during infectious processes. The increase is secondary to accelerated hepatic synthesis and release of ceruloplasmin, the principal copper-binding protein. This response appears to have potential value with respect to host defensive mechanisms. Serum copper and ceruloplasmin values remain elevated for a week or more during early convalescence.

IV.B.7.f. ZINC. Zinc metabolism is also altered during acute infectious illnesses. Like iron, serum zinc moves rapidly from serum into the liver during the early stages of most infectious illnesses, but the depression of serum zinc values is not usually as great as that of iron. Unlike iron, however, a zinc-binding metallothionein protein must be synthesized rapidly within hepatic cells in order to sequester the zinc. It is postulated that this extremely rapid adaptive process is of positive value in terms of host survival. In addition, as illness progresses, zinc balances can become negative as a result of diminished dietary intake of the metal along with increased losses in urine, feces, and sweat.

IV.B.8. VITAMIN REQUIREMENTS

Ever since the discovery of vitamins, research efforts and clinical trials have been used to test the attractive hypothesis that the ability of a host to resist infection is related to vitamin nutrition. Acute infections are followed in some instances by the onset of classic vitamin A deficiency, beriberi, pellagra, or scurvy (14). Such complications generally occurred in patients whose antecedent nutritional status was either unknown or poor. Blood concentrations of several vitamins, such as A, B_6, or C, may decline during acute bacterial and

viral illnesses, malaria, or chronic tuberculosis. Depressed concentrations of several vitamins in blood or tissues have also been reported in a variety of experimental infections in laboratory animals (14).

In contrast, when healthy volunteers were given normal recommended daily amounts of vitamins throughout the course of a mild viral illness, relatively little change was seen in either the urinary excretion or blood concentrations of most vitamins (3). However, an increased excretion of urinary riboflavin in these subjects began coincidentally with the onset of fever. The losses of riboflavin increased in magnitude during the early convalescent period and could be explained by the negative nitrogen balance.

Despite the paucity of detailed information concerning the rate of utilization or metabolic fate of vitamins in body stores during an infectious process, there can be no doubt that the metabolic actions of many vitamins are required to activate various host responses. The adrenal content of vitamin C is depleted during active steroidogenesis. The group B vitamins, vitamin C, and folate all contribute to the adequacy of phagocytic activity by host cells. A number of vitamins, including A, B_1, B_2, B_3, B_6, B_{12}, E, and folate, contribute in maintaining the complex immune functions of B- and T-lymphocytes and macrophages. The antioxidant activity of vitamin E may help protect cellular lysosomes in leprosy. Absorption of B_{12} is impaired by competition from fish tapeworms within the gut of infested patients, and the absorption of fat-soluble vitamins, folate, and B_{12} may also be impaired transiently in patients with enteric infections or parasitic infestations.

The antimicrobial drugs can also influence vitamin metabolism. Isoniazid, for example, has been thought to induce peripheral neuropathy

in some tuberculous patients by causing a deficiency of vitamin B_6. Pyridoxine supplementation has therefore been suggested for patients taking isoniazid. On the other hand, patients with tuberculosis may become overly sensitive to the normal action of vitamin D and become hypercalcemic, as in sarcoidosis.

Normal quantities of vitamins and other nutrients help to maintain host resistance at optimal levels. A mounting body of evidence suggests that many individual nutrients are each essential for maintaining the normal function of host immune responses. In contrast, deficiences, excesses, or imbalances of single nutrients may be harmful. Some immunological benefit has been shown in animal studies involving modest increases of dietary vitamin E and selenium. However, no evidence is yet available to show that megavitamin therapy benefits man by improving resistance against the invasion and proliferation of infectious microorganisms. Nevertheless, this prophylactic or therapeutic concept continues to intrigue both lay and scientifically trained individuals. Arguements have been widely publicized concerning the possible prophylactic value of taking vitamin C in massive doses. In contrast, the carefully prepared statement of the American Academy of Pediatrics Committee on Drugs (8) points out that there is no acceptable scientific evidence that ascorbic acid prevents the common upper respiratory viral infections.

Based on evidence presently available, practicing physicians should employ vitamins in normally recommended doses throughout the course of an infectious illness, or at most, should increase doses one- or two-fold to cover the possibility that vitamins may be metabolized (or excreted) in increased amounts during hypermetabolic states. The scientific evidence needed to justify megavitamin therapy in the treatment or prevention of infectious illnesses does not exist.

IV.C. POSSIBLE USE OF NEW ALIMENTATION TECHNIQUES DURING INFECTION

Techniques developed to meet the unusually large nutritional requirements of severely burned or traumatized patients now allow surgeons to provide the total daily caloric requirements despite the presence of hypermetabolic states. The technique of total parenteral feeding is described in other chapters (see Chs. 11, 12). Another technique for supplying nutrients involves using a constant-drip gavage of a chemically defined diet. Gavage is accomplished through thin-walled nasogastric catheters; the procedure has been termed "enteral hyperalimentation." Balanced free amino acid and carbohydrate mixtures, when given at proper concentrations and rates, can be fully absorbed in the upper intestine with a minimum of digestive work, and gavage can therefore be used in patients with lower intestinal lesions. Either technique carries certain risks that must be balanced against potential benefits.

In individuals whose nutritional stores have been depleted by severe disease or a compex surgical problem, secondary sepsis is a relatively common complication. It is generally difficult, if not impossible, to control or eliminate the septic process in such patients, even with the most vigorous utilization of normally appropriate and effective antibiotics. In contrast, when total parenteral alimentation is used to provide adequate nutritional support, many patients become free of fever, clear their blood and tissues of the invading microorganisms, and heal their surgical lesions.

The correction of nutritional deficiencies in patients with severe septic complications appears to permit host defensive mechanisms to regain their functional adequacy. It is therefore reasonable to consider the possible usefulness of total parenteral nutritional support for

overwhelming infections of a primary nature. Because of the technical need to infuse hypertonic solutions via chronically implanted central venous catheters, the process is not without danger. Microorganisms can gain access to the body through or around the catheters, and thrombus formation can be initiated within central veins. Early experiences with techniques of total parenteral nutrition were frequently complicated by bacterial or fungal contamination of the catheter, infusion solutions, or catheter entry sites. In addition, hyperosmolality caused by the infused nutrients can produce an osmotic diuresis with dehydration and, further, may cause impaired function of phagocytic cells. Hypertonic glucose concentrations may also disturb phagocytic functions. Severe hypophosphatemia can develop in patients receiving total parenteral alimentation; this has been shown to reduce leukocytic ATP content and to produce a marked depression in chemotactic, phagocytic, and bactericidal activities of granulocytes. Fluid overload must also be avoided. The potential value of "enteral hyperalimentation" must also be weighed on the basis of its potential dangers, which include induction of diarrhea, regurgitation, aspiration, changes in gut flora, and hyperosmolar dehydration.

Despite the potential dangers of these newer forms of nutritional therapy, patients with severe gram-negative bacterial sepsis or long-standing infectious processes may benefit by their usage. Life-threatening septic processes due to opportunistic microorganisms can often be eliminated if appropriate antimicrobial therapy is supplemented by vigorous nutritional measures. Such demonstrations are highly instructive, for they point out the value of nutritional therapy in an unequivocal manner. On the other hand, this form of nutritional support has not been adequately studied in life-threatening acute viral

infections, and the dangers could outweigh any potential advantages. If the acute stages of a short-term hypercatabolic infectious process make it impossible to maintain an adequate daily intake of energy and other nutrients, the resulting losses should be made up quickly in the early convalescent period when the problems of fever and anorexia have disappeared.

IV.D. POST-ILLNESS NUTRITIONAL ADJUSTMENTS

Infection-induced changes in the nutritional status of a subject, including the long-term depletion of body nutrients, are potentially reversible conditions. The full restitution of nutritional deficits that result from even a mild, self-limited infection of relatively brief duration may require several weeks of convalescence. The prolonged periods required for reconstituting body pools of essential nutrients following an infection resemble the prolonged periods of convalescence necessary after severe trauma or operative procedures. Thus, careful attention must be paid to the maintenance of optimal nutrient intakes during convalescence from an infection (1, 7, 9).

With the cessation of fever and anorexia, the early convalescent period represents a "nutritional window" that should be used to replace lost body nutrients. Some patients develop hyperphagia for several days, making the replacement of nutrients an easy task. In nutritionally depleted children, the nutritional aim should be to obtain "catch-up" growth, with the mother having a key role for achieving this objective (1, 9, 15). Good medical practice requires that patients be instructed about the need for maintaining a nutritional program that will allow for the reconstitution of measured or suspected losses.

Although nutritional therapy during convalescence should aim to correct deficits incurred during an infection, the temporary presence of these deficits can predispose a patient to secondary infections or weaken his resistance against an invasion by other virulent microorganisms. Body nutrient stores and the functional capabilities of host defensive mechanisms are at their lowest points in the days immediately after fever has abated. This problem is greatest in infants and small children whose nutritional requirements for growth are superimposed on nutritional needs for the maintenance of body homeostasis or for the reconstitution of nutrient stores after an infection. Thus, in the growing child, an infection often creates nutritional deficits that lead to new problems with secondary infections. Such synergistic cycles are the rule rather than the exception in children who suffer from preexisting deficits of protein, calories, or both (1, 9). Nutritional therapy in early convalescence may be life saving by reversing the cycle of infection, further malnutrition, and reinfection.

V. STRATEGIES FOR PREVENTION

V.A. NON-NUTRITIONAL

Non-nutritional approaches have been highly effective in lowering the incidence of many diseases, including the historic scourges of mankind. For example, the widespread utilization of vaccines has been of major importance in helping to control or prevent infectious diseases, especially those of viral origin. The development of toxoids has been of further help in blocking the toxicity of such diseases as diphtheria and tetanus. Improvements in sanitation and various environmental measures have gone far to eliminate water-borne and food-borne infectious

diseases and to virtually eradicate arthropod-borne infections, e.g., yellow fever and malaria, in the highly developed nations. A combination of effective antibiotic therapy and case-finding measures to identify carriers has helped to reduce the incidence of tuberculosis and the venereal diseases. Although none of these measures can entirely prevent infectious diseases, their implementation has proven to be of inestimable value in changing the patterns of disease incidence within the past century.

V.B. NUTRITIONAL

Evidence derived from laboratory studies, clinical observations, and field investigations, suggests that the ability of the human or animal host to resist infection reaches optimal levels when host nutritional status is adequate and there are no overt or borderline nutritional deficiencies. Chronic malnutrition predisposes the infants and children in many parts of the world to life-threatening infections (9). This problem is also seen in the elderly, and in hospitalized patients suffering from severe medical or surgical illnesses (7).

On the other hand, an overabundance of some nutrients may be harmful and may, in fact, increase host susceptibility to infection. Obesity causes an increase in susceptibility to many infections in humans and laboratory animals (12). If excesses of minerals, trace elements, or vitamins reach toxic levels, the host's ability to defend against certain microbial invaders is impaired. Thus, body nutrient stores should be adequate, but not excessive, if all aspects of normal host defensive mechanisms are to function optimally.

V.C. EVIDENCE OF INTERACTION

An impaired nutritional status generally lessens the ability of host defensive mechanisms to prevent infectious illnesses. This type of interaction is best exemplified by impairments in host immune mechanisms that may accompany various forms of malnutrition (15). Impaired immunologic functions are seen most commonly in children with nutritional deficits of proteins, calories, or both, but they occur as well in adults who develop acute nutritional losses as a result of serious disease or surgical procedures. Impaired immune function has also been recognized in individuals with deficiencies of single vitamins (A, B_6, B_{12}, folate) or other nutrients (iron, zinc).

The increased incidence and severity of infectious diseases in malnourished individuals can best be explained by functional inadequacies of both immunologic and nonspecific systems of host defense. Subtle-to-marked derangements develop in virtually every facet of immunologic function that has been studied in patients with nutritional inadequacies.

The immunologic abnormalities due to malnutrition can usually be corrected by nutritional therapy, but animal studies suggest that some residual immunodeficiency may persist.

The ability to synthesize new proteins from amino acid precursors is a key necessity for producing either cellular or humoral immunity. Protein synthesis is also a basic requirement for maintaining nonspecific host defensive mechanisms, including the formation of phagocytic cells as well as their ability to mobilize and function. In protein-energy malnutrition, competition appears to exist among tissues that need amino acids for growth, maintenance of body homeostasis, diverse subcellular

activities, and immunogenesis. With such nutritional deprivations, body systems are unable to function optimally, and even a mild infection can stimulate an excessive body demand for scarce nutrients.

The cellular uptake of free amino acids is governed by their interacellular and extracellular concentrations as well as by hormonal and metabolic influences on amino acid receptor sites of cell surface membranes. The body does not appear to possess a centralized control mechanism or specific priority system to distribute individual amino acids equitably among various body cells. In a malnourished individual, the lack of a priority-defining mechanism seems to work to the detriment of cells of the lymphoid system which are responsible for immunogenesis and immunocompetence. Lymphoid cells must therefore compete with amino-acid hungry cells, such as those of muscle and liver, or with cells needed for tissue growth and repair.

A deprivation of body protein, with or without a coexisting deficit in energy intake, will lead to widespread anatomic abnormalities of lymphoid tissues. These anatomic changes include thymic and tonsilar atrophy, generalized lymphoid hypoplasia, and a reduction in the number of circulating blood lymphocytes. Similar anatomic changes may also occur when malnutrition involves certain single essential micronutrients.

Malnourished individuals may show a depressed antibody response after immunization with widely used vaccines. Some of the differences in response during malnutrition may be related to the antigenic nature and potency of a vaccine. It has been found that children with kwashiorkor who respond normally to a live polio vaccine may show a depressed antibody response to a live yellow fever vaccine. Children with kwashiorkor also show an impaired ability of their lymphocytes to respond to the mitogenic actions of phytohemagglutinin. Deficient

persons may fail to generate a delayed dermal hypersensitivity reaction against skin test antigens to which they were previously sensitized. Malnutrition also leads to impaired phagocytic activity or bactericidal capability of peripheral blood neutrophils and to diminished concentrations of most components of the complement system in serum.

V. FINAL EVALUATION

Approaches to the nutritional management of infectious disease problems can be summarized in a series of guidelines and therapeutic steps in most clinical situations.

Body defensive mechanisms that prevent or minimize infectious illnesses seem to function best when a patient is in normal nutritional balance. Deficits or excesses of nutrients may predispose to an increased risk of infection or to an infection of increased severity.

Although nutritional management during the therapy of most infections falls into the realm of secondary or supportive care, on rare occasions immediate correction of a nutritional abnormality may be of life-saving importance. It should then take precedence in the management of the illness. These emergency situations generally involve the correction of severe fluid and electrolyte or acid-base abnormalities. Severe hypoglycemia or anoxia must also be corrected without delay.

In most nonviral infections the selection of an appropriate antimicrobial drug and dosage schedule, or a combination of drugs should form the major bulwark of therapy. In a previously healthy person, the nutritional management of infection should aim at preventing or lessening the absolute and functional forms of anticipated nutrient losses. Control of fever will lessen the ultimate severity and duration of nutrient wastage and can thus be categorized as a preventive measure

in nutritional management. In addition to the control of fever, efforts should be made to supply adequate amounts of key nutrients to meet body needs during the illness.

Maintenance of an adequate caloric intake is the most important single need. Adequate but not excessive intakes of protein (or other amino acid sources) and vitamins are important secondary goals. Adequate nutritional therapy may require the use of parenteral infusions to meet the caloric needs of patient with protracted illnesses. In patients who are already severely malnourished, the use of parenteral nutrients may make it possible to control and eliminate septic processes that cannot be managed by antibiotics alone. The administration of specific minerals or trace elements is not generally required during an acute, brief infectious illness.

Nutritional deficiencies begin to develop in infections of even short duration and become clinically important if febrile patients are unable to consume dietary nutrients for more than a few days. Should an infectious process become chronic, it will be accompanied by a more compex variety of nutritional inadequacies, some of which are difficult to correct until the infectious process can be controlled or eliminated.

Because of their nutritional deficits, patients who recover from an acute infectious illness face greater-than-normal danger from occurrence of secondary infections during early convalescence. This danger can be lessened by vigorous attempts to repair or correct nutritional deficits suffered during the acute phases of illness.

Finally, in patients with overt preexisting nutritional defects, corrective nutritional therapy should lead to a reversal of abnormal host defensive functions and lessen the danger from superimposed new infections.

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